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Empirical ethics: the "missing link" in incidental findings recommendations

Response to Clayton *et al.*'s "Addressing the Ethical Challenges in Genetic Testing and Sequencing of Children"

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While Clayton *et al*. (2012) rightly highlight the differences and tensions in the ethical justifications utilized by what they refer to as the AAP/ACMG and ACMG ES/GS recommendations, they fall short in explaining the source of these differences. Only once the source of the differences is correctly identified and explored, can the implications of tensions between the two sets of recommendations be addressed: that is, whether or not they need agree.

We argue that the differences largely rest on the implied methodologies underlying the two guidelines. The AAP/ACMG recommendations make use of the results of empirical ethics involving a range of stakeholders, a methodology which the ACMG ES/GS guideline ignores. Clayton *et al*. describe how the former recommendations on predictive genetic testing and screening of children situate themselves within the professional tradition and empirical research on how adults and families respond to predictive testing. The latter recommendations in contrast make no reference to either this professional tradition or empirical research in justifying their position. These recommendations appear to have been inspired mainly by the views of some medical professionals, without taking into account all the other stakeholders who will be impacted by the guidelines. This lacuna severely weakens the persuasiveness of the ACMG ES/GS recommendations.

So-called "empirical ethics" involves bringing general principles and particular judgements or experiences into conversation with each other, with the aim of advancing in ethical reflection (Schotsmans, 1999). Neither the normative nor the empirical should be given undue weight, but both should be allowed to inform and challenge each other. A prerequisite is an accurate description of the context (Borry *et al*., 2004). The context of the AAP/ACMG recommendations is a positive family history, in which both children and adults will know that they can choose to request testing once they are over majority. The ACMG ES/GS recommendations assume no positive family history. Consequently, the disclosure of an incidental finding discovered in the child is the only way that the rest of the family will know that they might want to get tested. (Incidentally, if a positive family history were to be present, the context reverts to one similar to that of the AAP/ACMG recommendations; this would only come to light if clinicians and laboratory staff were in communication about the patients, a possibility which does not seem to be explored in the present guidelines.) Other aspects of the context remain to be specified. For instance, are we to assume the current situation, where ES/GS is mainly ordered for children in cases of serious developmental disabilities or congenital anomalies, i.e. in cases where the family already has to deal with a severe clinical condition? There is additionally the justice and practical question of who will finance the extra laboratory work-up. It will be helpful to get some idea of the scale of impact of the guidelines, by looking for instance at the expected proportion of actionable, pathogenic incidental findings based on current, admittedly limited databases (e.g. Dorschner *et al*., 2013), and by clarifying how far investigations of relatives should go to determine the clinical significance of a suspected incidental finding (Crawford *et al*., 2013).Ethically sound guidelines should also keep in mind the consequences at each step of the disclosure process: from laboratory to clinician, from clinician to parents, and, perhaps most crucially, from parents to children.

Once the context has been delimited in as detailed a way as possible, normative and empirical explorations can be brought into the conversation. While there are numerous guidelines and normative position papers arguing against predictive testing of children for adult-onset disorders, which the AAP/ACMG recommendations make use of, there are other arguments encouraging early predictive testing (Rhodes, 2006). The accompanying technical report of the AAP/ACMG allows for exceptions depending on the family's motivation, context, and understanding. The question is whether the exception can ever become the rule. The ACMG ES/GS recommendations take the family as the basic unit of clinical care rather than the child. Some recent clinical literature supports viewing incidental findings in children of adult-onset conditions as family matters (May *et al*., 2013). Another relevant line of inquiry is whether the so-called "right not to know" that some parents or children (or future adult children) may wish to claim, is valid in the case of actionable, pathogenic incidental findings. Naysayers include those who argue that such ignorance can be harmful, those who argue that such ignorance is opposed to autonomy, and those who argue that the discussion should move to harms and benefits at an inter-subjective level (Wilson, 2005). The normative ethical work is yet to be done, not just to shore up arguments defending the ACMG's latest position but also to justify the apparent radical break with former recommendations.

Helpful in this process are empirical investigations of the values and motivations relevant to stakeholders in the context of pediatric genetic incidental findings. Stakeholders include medical professionals, laboratory personnel, parents, families, and children (if possible). Such investigations can clarify the weighting of various normative positions. In this respect, it is not enough simply to know whether parents for instance would accept the consequences of the ACMG ES/GS recommendations, but also their reasons for doing so. Two recent comparable interview studies suggest that most parents would appreciate the disclosure of adult-onset, actionable, pathogenic incidental findings discovered in their children (Sapp *et al*., 2013; Christenhusz *et al*., 2014). More

interesting from an ethical point of view is how parents justified their positions, as well as the sorts of justifications used by those opposed to disclosure, and the ethical weight that can be ascribed to each type of argument. Also interesting is our finding that some of those who said that they did not want certain results disclosed to them, found it unacceptable if the doctor would know something about their child that they did not (Christenhusz *et al*., 2014). In other words, they would rather forgo their "right not to know," than that the doctor would know a certain unexpected result and not disclose. A finding like this deserves more investigation. One response is that medical professionals should be very sure about what they want to discover about their patients; after all, what they do not know themselves, they cannot disclose.

We have argued that the main difference between the AAP/ACMG and ACMG ES/GS recommendations lies in the "missing link" of empirical ethics, and have attempted to show how normative ethical reflections and empirical investigations could be brought together to flesh out the ACMG ES/GS recommendations. If it can be shown that different ethical arguments are valid for the two sets of recommendations, based on justifiably different contexts, it can then be argued that these evolving, ethically sound, internally consistent guidelines need not agree with each other.

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